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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/679,147	10/05/2000	Tomoki Todo	066683/0188B	7711

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EXAMINER	
BECKERLEG, ANNE M	
ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 06/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/679,147	Applicant(s) TODO ET AL.	
	Examiner Anne Marie Becherleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Applicant's amendment and response including exhibits received on 4/4/02 have been entered. New claims 33-47 have been added. Claims 1-47 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Applicants have overcome the objection to claims 15 and 27, and pages 10 and 11 of the specification by providing clean copies of pages 10 and 11 with appropriate margins.

Claim Rejections - 35 USC § 112

The rejection of original claims 1-32 and new claims 33-47 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant rejection for reasons of record as discussed in detail below.

The applicant arguments have been addressed in the order presented. The applicant argues that low MHC class I expression on tumor cells is not an obstacle to the current methods of treatment as this invention secretes the costimulatory molecule and does not require MHC class I presentation. The applicant has apparently misunderstood the examiner's concerns regarding the the ability of the target tumor cells to express immune related molecules. The previous office action stated that the art at the time of filing teaches that tumors evade immune responses by a variety of mechanisms including down-regulation of TAP and MHC-encoded proteasome components, loss of antigenic epitopes by either lack of expression or mutations, loss of functional β_2m expression , and loss of particular MHC class I alleles (Restifo et al (1993) J. Immunother., Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). The loss or mutation of any of these molecules would prevent the tumor from being recognized by the tumor specific cytotoxic T cells. Thus, the issue here is that many tumors lack expression of TAP molecules, proteosome components, and/or MHC molecules, and thus cannot present tumor antigen on the cell surface (Restifo et al.). In the absence of sufficient levels of peptide/MHC on the cell surface, the tumor cannot be targeted by activated T cells. While the level of MHC class I expression on the Neuro2a cells is may be low enough to prevent direct activation of T cells by the tumors cell themselves, the level of peptide/MHC on the cell surface has been demonstrated to be sufficient to allow lysis of the cells by peptide-specific activated T cells. Furthermore, the reason this issue was raised in the previous office action was to demonstrate that there are many art recognized problems with cancer immunotherapy. Also note that the office did not rely solely on this issue to

demonstrate the unpredictability of cancer gene therapy. The office also provided evidence that the skilled artisan at the time of filing considered gene therapy of cancer unpredictable based on the limitations associated with current vector systems, and the unpredictability of targeting specific cell types in vivo.

The applicant further argues that the office has used an inappropriate standard, i.e. FDA requirements and clinical trial data, to evaluate the enablement of the instant invention. In particular, the applicant states that therapeutic or clinical data is not required in order to obtain a patent, and that FDA standards of effectiveness are inappropriate in regards to the patentability of the instant claims. In response, it is noted that the office has neither requested nor required clinical trials and that FDA standards of effectiveness have not been applied to the instant case. The office has analyzed the specification in direct accordance to the factors outlined in In re Wands, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. It is also noted that case law including the *Marzocchi* decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see In re Marzocchi 169 USPQ 367, and Ex parte Sudilovsky 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Ultimately, 35 U.S.C.

§ 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970).

In regards to applicant's argument that Orkin does make some positive statements regarding immunotherapy of cancer, please note that Orkin et al., Verma et al., and Marshall et al., were all cited in the previous office action as evidence that the skilled artisan at the time of filing did not consider gene therapy of cancer as predictable based on the known limitations and problems associated with vector design and vector delivery. The fact that some success has been demonstrated and mentioned by Orkin et al. does not detract from the central teachings of these three references which clearly establish that currently available vector systems suffer from a number of problems including transiency of expression, inappropriate anti-vector immune responses, lack of transduction efficiency, and inability to target specific cells.

The applicant also argues that since the Neuro2a tumor is known in the art an a non-immunogenic tumor, the applicant's evidence regarding the treatment of the Neuro2a tumor with soluble B7-Ig enables the treatment of other tumor types. The previous office action stated that the specification is enabling for methods of reducing the growth of a solid neuroblastoma by intratumoral injection of a defective Herpes Simplex Virus (HSV) vector encoding a soluble B7-1-Ig fusion protein. In regards to the treatment of any and all types of tumors, please see the discussion above regarding art recognized problems in treating tumors using immunotherapy where the tumor is defective in antigen expression, processing and/or presentation. Further, the

references cited by applicants, i.e. Katsanis et al. and Heuer et al., are solely directed to the treatment of the Neuro2a tumor by tumor expression of membrane-bound B7. This evidence does not appear relevant to instant methods as the co-stimulatory used in these experiments is not soluble.

The applicant further argues that the office has not met provided sufficient evidence that the specification is not enabling for making and using any soluble co-stimulatory molecule according to the instant invention, citing *In re Wright* and *In re Bowen*. As discussed above, the office has analyzed the specification is direct accordance with the factors outlined in *In re Wands* and provided evidence in the form of both scientific arguments and cited publications in support of the instant finding of non-enablement for the full scope of applicant's claimed invention. In support of applicant's contention that the specification does provide guidance for making co-stimulatory molecules other than soluble B7, the applicant has provided several publications published before the instant filing date. The office concedes that the evidence provided, i.e. publications by Kato et al., Kanner et al., Noelle et al., and Hurtado et al., do demonstrate that it was within the skill of the artisan to make a soluble co-stimulatory molecule comprising the extracellular domain of the co-stimulatory molecule and IgG. However, the evidence does not provide enablement for making soluble co-stimulatory molecules that do not contain IgG, or for the use of any soluble co-stimulatory molecule/IgG fusion protein to activate therapeutic levels of anti-tumor specific T cells *in vivo*. Hurtado et al. and Noelle et al. disclose s4-1BBFc and sCD40Ig which in fact inhibit rather than activate T cells. Kato et al. discloses sCD2Ig and

sCD48Ig and their use in *in vitro* binding studies. Kato et al. provides no evidence regarding the ability of either fusion protein to actually stimulate T cells or to treat tumors *in vivo*. Kanner et al. teaches sLFA3Ig. While Kanner et al. does teach the use of sLFA3Ig for stimulating T cells *in vitro*, Kanner et al. clearly discloses that effective stimulation requires cross-linking of the sLFA3Ig. Applicant's claims are not so limited. Thus, the combined teachings of provided publications demonstrate that while soluble fusion proteins comprising a co-stimulatory molecule and Ig can be made, it is unpredictable whether the resulting protein is capable of actually stimulating T cells either *in vitro* or *in vivo*, particularly in the absence of cross-linking.

In regards to the unpredictability of using any and all vectors in applicant's instant invention, the applicant argues that much was known about various gene therapy vectors at the time of filing and that many clinical trials were in progress using vector therapy as of 1999. The applicants cite Fry et al. and Roth et al. in support of this argument. The previous office action stated that the specification also does not provide an enabling disclosure for using any vector/promoter combination to express therapeutic amounts of B7-1-Ig *in vivo*, citing Verma et al., Marshall et al., and Orkin et al. Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the need for appropriate vector/promoter combinations for a particular cell type. The applicant has not specifically addressed these issues. Further, the articles cited by the applicants support the views expressed by Verma, Marshall, and Orkin. For instance, both Fry and Roth provides tables which outline the problems associated with each type of vector system currently in use, and specifically

discuss the fact that the use of adenoviruses are limited by their generation of anti-vector immune responses, and that transiency of expression relating to promoter selection is a problem area which require further research and experimentation (Fry et al., pages 12-20, and Roth et al., pages 24-28). On page 20, Fry concludes that, "with regards to gene therapy, the main focus of research is the development of new gene transfer vectors that are more efficient and safer, in an effort to overcome the major hurdles that are currently associated with clinical gene therapy" (Fry et al., page 20, bridging paragraph). It is further noted that in addition to teaching the problems associated with vector delivery, Roth et al. also reiterates the teachings of Restifo et al. regarding tumor immunotherapy. On page 22, Roth et al. states that in regards to tumor immunotherapy that, "this approach may therefore require replacement of multiple genes within the tumor cell to elicit an effective immune response. It is also possible that, despite activation of the efferent arm of the immune response to tumor antigens, ineffective transport mechanisms may result in an antigen density too low to be recognized by the cytotoxic effector cells" (Roth et al. page 22, bridging paragraph). Thus, contrary to applicant's assertion, the skilled artisan clearly considered gene therapy of cancer, and particularly tumor immunotherapy to be unpredictable at the time of filing.

Finally, in regards to routes of delivery, the applicant argues that there is no evidence of record that other delivery methods would not work. On the contrary, the previous office action provided substantial evidence regarding the lack of predictability in targeting vector delivery and

gene expression to particular cell types *in vivo*, citing Deonarian and Miller. The applicant has not provided any arguments regarding this evidence.

Thus, based on the art recognized unpredictability of achieving therapeutic levels of gene expression using currently available vectors at the time of filing, the unpredictability of treating cancer using immunotherapy, the art recognized unpredictability of targeting vectors to specific cell types *in vivo*, the lack of guidance for using nucleic acids encoding soluble co-stimulatory factors other than B7-1-Ig for the treatment of tumors, the heterogeneity of tumors in regards to their ability to express antigen and stimulate T cells, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to treat any and all tumors by administering any vector encoding any soluble co-stimulatory factor using any route of administration.

The rejection of original claims 1-22, 24-31 and new claims 41-47 under 35 U.S.C. 112, second paragraph, as being indefinite for the use of the term "tumor-related cells " is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant rejection for reasons of record as discussed in detail below.

The applicant states that "tumor-related cells" are defined as cells in and around the tumor such as endothelial cells, mesechymal cells, and immune cells. This definition does not overcome the indefiniteness of the term "tumor-related" in relation to a cell. The term "related" is extremely relative. The terminology does not clearly describe how the cells are related to the tumor. For instance, endothelial cells, mesenchymal cells, and immune cells exist throughout the body and are

not located and/or do not associate exclusively with tumor cells. Since the applicant appears to intend the claims to read on cells in the vicinity of the tumor, it is suggested that the claims be amended to recite "cells in the vicinity of the tumor".

Claim Rejections - 35 USC § 102

The rejection of original claims 1, 7-11, 17-25, 28-32 under 35 U.S.C. 102 (e) as being anticipated by U.S. Patent No. 6,310,045, hereafter referred to as Barber et al., is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant rejection for reasons of record as discussed in detail below.

The applicant argues that Barber et al. does not teach a soluble costimulatory factor that is normally expressed on the membrane of antigen presenting cells and required for T cell stimulation. Applicant's claims as written do not limit the soluble costimulatory molecule to a molecule which is normally expressed on the membrane of antigen presenting cells. The claims as written simply recite a "soluble costimulatory factor". The previous office action states that IL-2 was well characterized at the time of filing, and was recognized by the art as a co-stimulatory factor based on its ability to act as a second signal for T cell activation. IL-2 is also a soluble protein. Thus, Barber et al. does in fact teach all the limitations of the invention as claimed.

The rejection of original claims 23 and 32 under 35 U.S.C. 102(b) as being anticipated by Hollenbaugh et al. is maintained. Please note that the applicant's have erroneously indicated that claims 1, 7-11, 17-22, 24-25, and 28-31 have been included in this rejection. The rejection of record was limited to claims 23 and 32. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant rejection for reasons of record as discussed in detail below.

The applicant argues that Hollenbaugh et al. does not teach that the vector is to be used for gene therapy. The applicant's claims are composition claims, and do not specifically recite a "gene therapy vector". The applicant claims a pharmaceutical composition comprising a vector encoding a soluble co-stimulatory factor and a pharmaceutically accepted carrier. Furthermore, the previous office action stated that in regards to the intended use of this composition as a "pharmaceutical" composition, it is noted that the intended use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto* , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). The applicant has not presented any evidence that the vector taught by Hollenbaugh et al. is structurally different from the applicant claimed composition.

The rejection of original claims 23 and 32 under 35 U.S.C. 102(a) as being anticipated by Sturmhoefel et al. is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant rejection for reasons of record as discussed in detail below.

The applicant argues that Strumhoefel does not teach that the vector is to be used for gene therapy. The applicant's claims are composition claims, and do not specifically recite a "gene therapy vector". The applicant claims a pharmaceutical composition comprising a vector encoding a soluble co-stimulatory factor and a pharmaceutically accepted carrier. Furthermore, the previous office action stated that in regards to the intended use of this composition as a "pharmaceutical" composition, it is noted that the intended use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto* , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). The applicant has not presented any evidence that the vector taught by Sturmhoefel is structurally different from the applicant claimed composition.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé